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PCT

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C12N 9/12, 5/00, 1/20, 15/00, C12P 21/06, 19/34, C07K 1/00, C07H 21/02, 21/04</p>	<p>A1</p>	<p>(11) International Publication Number: WO 98/01543 (43) International Publication Date: 15 January 1998 (15.01.98)</p>
<p>(21) International Application Number: PCT/US97/12297 (22) International Filing Date: 8 July 1997 (08.07.97) (30) Priority Data: 08/676,967 8 July 1996 (08.07.96) US (71) Applicant: TULARIK, INC. [US/US]; Two Corporate Drive, South San Francisco, CA 94080 (US). (72) Inventor: CAO, Zhaodan; Two Corporate Drive, South San Francisco, CA 94080 (US). (74) Agent: OSMAN, Richard, Aron; Science & Technology Law Group, Suite 3200, 268 Bush Street, San Francisco, CA 94104 (US).</p>	<p>(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i></p>	
<p>(54) Title: HUMAN TELOMERASE GENE</p> <p>(57) Abstract</p> <p>The invention provides methods and compositions relating to a human telomerase and related nucleic acids, including four distinct human telomerase subunit proteins called p140, p105, p48 and p43 having human telomerase-specific activity. The proteins may be produced recombinantly from transformed host cells from the disclosed telomerase encoding nucleic acids or purified from human cells. Also included are human telomerase RNA components, as well as specific, functional derivatives thereof. The invention provides isolated telomerase hybridization probes and primers capable of specifically hybridizing with the disclosed telomerase gene, telomerase-specific binding agents such as specific antibodies, and methods of making and using the subject compositions in diagnosis, therapy and in the biopharmaceutical industry.</p>		

Human Telomerase Gene

INTRODUCTION

Field of the Invention

5 The field of this invention is a human gene encoding an enzyme involved in cell replication.

Background

10 DNA at chromosome ends is maintained in a dynamic balance of loss and addition of telomeric simple sequence repeats. Sequence loss occurs during cell replication, in part from incomplete replication of chromosome termini by DNA-dependent DNA polymerase. Telomeric repeat addition is catalyzed by the enzyme telomerase: a ribonucleoprotein enzyme which uses a short region within the RNA as a template for the polymerase reaction. Although cells can maintain a constant number of telomeric repeats by balancing repeat loss and addition, not all cells do so. Human germline and cancer
15 cells maintain a constant number of telomeric repeats, while normal human somatic cells lose telomeric repeats with each cycle of cell division. Cells which do not maintain stable telomere length demonstrate a limited proliferative capacity: these cells senesce after a number of population doublings correlated with the erosion of telomeres to a critical minimum length.

20 Because normal somatic cells do not appear to express or require telomerase and do not maintain chromosome ends, and because all or almost all cancer cells express high levels of telomerase activity and maintain chromosome ends, molecules that inhibit or alter telomerase activity could provide effective and non-toxic anti-cancer agents.

Similarly, inhibition of telomerase in parasitic or infectious agents (e.g. trypanosomes, fungi, etc.) could provide a specific approach for reducing the viability or proliferation of these agents. Conversely, activation of telomerase in proliferation-restricted cells (such as normal somatic cells of the blood, vasculature, liver, skin, etc.) could provide a mechanism for promoting additional proliferative lifespan.

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Relevant Literature

Purification of telomerase from the ciliate *Tetrahymena* and cloning of genes encoding two protein components of the enzyme is reported in Collins et al. (1995) Cell 81, 677-686 and copending US patent application No. 08/359,125, filed 19 DEC 1994. Literature relating to human telomerase include Kim et al. (1994) Science 266, 2011-2014; and Feng et al. (1995) Science 269, 1236-1241. Literature relating to telomerase template modifications include Autexier et al. (1994) Genes and Devel 8, 563-575; Yu et al. (1991) Cell 67, 823-832; and Yu et al. (1990) Nature 344, 126-132. The Washington University-Merck EST Project contains an EST, reportedly deposited by Hillier et al. on Nov 1, 1995, which has sequence similarity with the 3' end of SEQ ID NO:3, disclosed herein. For a general review, see Blackburn et al., Eds. (1995) Telomeres, Cold Spring Harbor Laboratory Press.

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SUMMARY OF THE INVENTION

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The invention provides methods and compositions relating to a human telomerase and related nucleic acids. Included are four distinct human telomerase subunit proteins, called p140, p105, p48 and p43 and telomerase protein domains thereof having telomerase-specific activity. The proteins may be produced recombinantly from transformed host cells from the subject telomerase encoding nucleic acids or purified from human cells. Also included are human telomerase RNA components, as well as specific, functional derivatives thereof.

25

The invention provides isolated telomerase hybridization probes and primers capable of specifically hybridizing with the disclosed telomerase gene, telomerase-specific binding agents such as specific antibodies, and methods of making and using the subject compositions in diagnosis (e.g. genetic hybridization screens for telomerase transcripts), therapy (e.g. gene therapy to modulate telomerase gene expression) and in the

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biopharmaceutical industry (e.g. reagents for screening chemical libraries for lead pharmacological agents and nucleic acid polymerase reagents).

SEQ ID LISTING

- SEQ ID NO:1: p105 protein (amino acid sequence)
- 5 SEQ ID NO:2: p105 ambiguity maximized synthetic DNA
- SEQ ID NO:3: p105 natural cDNA (the coding region is bp 97-2370)
- SEQ ID NO:4: p105 E. coli optimized synthetic DNA
- SEQ ID NO:5: p105 mammalian optimized synthetic DNA
- SEQ ID NO:6: telomerase RNA
- 10 SEQ ID NO:7: telomerase RNA template region modification 1
- SEQ ID NO:8: telomerase RNA template region modification 2
- SEQ ID NO:9: telomerase RNA template region modification 3
- SEQ ID NO:10 p43 peptide (XXXEAAT[I/L]D[I/L]PQQGANK, where the three X's are indeterminant residues)

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DETAILED DESCRIPTION OF THE INVENTION

The invention provides isolated human telomerase proteins including human telomerase proteins p140, p105, p48 and p43, having molecular weights of about 140kD, about 105kD, about 48kD and about 43kD, respectively, as determined by polyacrylamide gel electrophoresis under denaturing conditions (Matsudaira and Burgess (1978) Anal Biochem 87, 386-396), and telomerase protein domains thereof. The telomerase proteins

20 comprise assay-discernable functional domains including RNA recognition motifs and subunit binding domains and may be provided as fusion products, e.g. with non-telomerase polypeptides. The human telomerase proteins of the invention, including the

25 subject protein domains, all have telomerase-specific activity or function.

Telomerase-specific activity or function may be determined by convenient *in vitro*, cell-based, or *in vivo* assays: e.g. *in vitro* binding assays, cell culture assays, in animals (e.g. immune response, gene therapy, transgenics, etc.), etc. Binding assays encompass any assay where the molecular interaction of a telomerase protein with a

30 binding target is evaluated. The binding target may be a natural intracellular binding target such as a telomerase subunit (e.g. another protein subunit or RNA subunit), a

substrate, agonist, antagonist, chaperone, or other regulator that directly modulates telomerase activity or its localization; or non-natural binding target such a specific immune protein such as an antibody, or a telomerase specific agent such as those identified in assays described below. Generally, telomerase-binding specificity is assayed by telomere polymerase activity (see, e.g. Collins et al. 1995, Cell 81, 677-686), by binding equilibrium constants (usually at least about 10^7 M^{-1} , preferably at least about 10^8 M^{-1} , more preferably at least about 10^9 M^{-1}), by the ability of the subject protein to function as negative mutants in telomerase-expressing cells, to elicit telomerase specific antibody in a heterologous host (e.g a rodent or rabbit), etc. In any event, the telomerase binding specificity of the subject telomerase proteins necessarily distinguishes ciliate telomerase, preferably distinguishes non-mammalian telomerases and more preferably distinguishes non-human telomerases. Exemplary telomerase proteins which are shown to have telomerase binding specificity include the telomerase RNA (e.g. SEQ ID NO:6) binding domains (e.g. RRM 1-4: SEQ ID NO:1, about residues 5-81, residues 115-192, residues 336-420, and residues 487-578, respectively), telomerase primer binding domains, nucleotide triphosphate binding domains and binding domains of regulators of telomerase such as nuclear localization proteins, etc. As used herein, a protein domain comprises at least 12, preferably at least about 20, more preferably at least about 40, most preferably at least about 80 residues of the disclosed respective SEQ ID NO.

The claimed human telomerase proteins are isolated or pure: an "isolated" protein is unaccompanied by at least some of the material with which it is associated in its natural state, preferably constituting at least about 0.5%, and more preferably at least about 5% by weight of the total protein in a given sample and a pure protein constitutes at least about 90%, and preferably at least about 99% by weight of the total protein in a given sample. The telomerase proteins and protein domains may be synthesized, produced by recombinant technology, or purified from human cells. A wide variety of molecular and biochemical methods are available for biochemical synthesis, molecular expression and purification of the subject compositions, see e.g. Molecular Cloning, A Laboratory Manual (Sambrook, *et al.* Cold Spring Harbor Laboratory), Current Protocols in Molecular Biology (Eds. Ausubel, *et al.*, Greene Publ. Assoc., Wiley-Interscience, NY) or that are otherwise known in the art. An exemplary method for isolating each of human telomerase protein p140, p105, p48 and p43 from human cells is as follows:

Several thousand (two to twelve thousand) liters of HeLa cells are grown in spinner culture. The cells are lysed by dounce homogenization in low-salt buffer to produce crude cell lysates. The lysates are supplemented with 15% glycerol and centrifuged at $125,000 \times g$ for 50 minutes to obtain a first soluble fraction enriched for telomerase activity (S-100 fraction). The S-100 fraction is adjusted to 0.2 M ammonium sulfate, bound to SP Sepharose

(Pharmacia), and developed with a gradient in sodium chloride, to obtain a second soluble

fraction enriched for telomerase (SP fraction). The SP fraction is adjusted to about 0.3-

0.4 M ionic strength and bound to Q Sepharose (Pharmacia), and developed with a

gradient in sodium chloride, to obtain a third soluble fraction enriched for telomerase (Q

fraction). The Q fraction is adjusted to about 0.3-0.4 M ionic strength, bound to

phosphocellulose (Whatman), and developed with sodium chloride, to obtain a fourth

soluble fraction enriched for telomerase (PC fraction). The PC fraction is adjusted to

about 0.3-0.4 M ionic strength, bound to 2'Omethyl RNA oligonucleotide immobilized on

streptavidin agarose (Sigma), and eluted with a electrophoresis sample medium

comprising 5% β -mercaptoethanol and 2% Sodium Dodecyl Sulfate to obtain a fifth

soluble fraction (2'Omethyl fraction). The 2'Omethyl fraction is separated by

polyacrylamide gel electrophoresis under denaturing conditions (Matsudaira and Burgess

(1978) Anal Biochem 87, 386-396) to obtain gel protein bands at a molecular weight of

about 140kD, 105kD, 48kD or 43kD having telomerase activity. The gel bands are

excised or blotted to obtain purified human telomerase proteins p140, p105, p48 and p43.

The subject telomerase proteins find a wide variety of uses including use in isolating, enriching for and concentrating telomerase RNA and telomerase proteins, as

immunogens, in the methods and applications described below, as reagents in the

biotechnology industries, and in therapy. Recombinant telomerase are used in many

applications where nascent oligonucleotides of predetermined sequence are desired. For

example, native nucleic acid molecules are labeled or extended at their 3' ends by addition

of a predetermined repeat sequence (for double-stranded oligonucleotides, both ends of

the molecule may be tagged). Oligonucleotides complementary to the repeat are then

used to amplify, sequence, affinity purify, etc. the nucleic acid molecules. The use of a

repeat sequence for 3' end tagging improves specificity and provides sequence alternatives

compared with non-templated enzymes presently available for this purpose, e.g. terminal

transferase. Repeats encoding restriction enzyme sites provide repeat tagging to facilitate cloning and the use of telomerase alleviates the restrictive conditions required for optimal ligation with available ligase enzymes. Telomerase also finds use in regulating cell growth or increasing cell density tolerance; for example, cells contacted with an effective amount of exogenous telomerase to overcome the growth control limitation otherwise imposed by short telomere length. Telomerase may be introduced, expressed, or repressed in specific populations of cells by any convenient way such as microinjection, promoter-specific expression of recombinant enzyme, targeted delivery of lipid vesicles, etc. Advantageously, only a brief period of telomerase activity is required to allow many generations of continued proliferation of the contacted cell, due to the ability of telomerase to extend telomeres in one cell cycle by more sequence than is lost with each cell division.

The invention provides natural and non-natural human telomerase-specific binding agents including substrates, agonist, antagonist, etc., methods of identifying and making such agents, and their use in diagnosis, therapy and pharmaceutical development. For example, human telomerase-specific agents are useful in a variety of diagnostic and therapeutic applications. Novel human telomerase-specific binding agents include human telomerase-specific receptors, such as somatically recombined protein receptors like specific antibodies or T-cell antigen receptors (see, e.g. Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory) and other natural intracellular binding agents identified with assays such as one-, two- and three-hybrid screens, non-natural intracellular binding agents identified in screens of chemical libraries such as described below, etc. Agents of particular interest modulate human telomerase function, e.g. human telomerase antagonists and find use methods for modulating the binding of a human telomerase or telomerase protein to a human telomerase binding target.

For diagnostic uses, the binding agents are frequently labeled, such as with fluorescent, radioactive, chemiluminescent, or other easily detectable molecules, either conjugated directly to the binding agent or conjugated to a probe specific for the binding agent. Binding agents also find use in modulating the telomerase activity present in a cell. For example, isolated cells, whole tissues, or individuals may be treated with a telomerase binding agent to activate, inhibit, or alter the specificity of telomerase assembly,

localization, substrate interaction, or synthesis activity. Effectively treated cells have increased or decreased replication potential, or suffer from loss of proper telomere structure (resulting in lethality). These binding agents also find therapeutic use to control cell proliferation; for example, the uncontrolled growth of transformed cells (e.g. cancer cells) is managed by administration to the cells or patient comprising such cells of a telomerase binding agent which reduces telomerase activity. In contrast to many current chemotherapies, the present invention provides enhanced specificity of lethality, with minimum toxicity to dividing yet normal somatic cells.

The amino acid sequences of the disclosed telomerase proteins are used to back-translate telomerase protein-encoding nucleic acids optimized for selected expression systems (Holler et al. (1993) Gene 136, 323-328; Martin et al. (1995) Gene 154, 150-166) or used to generate degenerate oligonucleotide primers and probes for use in the isolation of natural telomerase encoding nucleic acid sequences ("GCG" software, Genetics Computer Group, Inc, Madison WI). As examples, SEQ ID NO:2 discloses an ambiguity-maximized p105 coding sequence encompassing all possible nucleic acids encoding the full-length p105 protein. SEQ ID NO:3 discloses a natural human cDNA sequence encoding p105, SEQ ID NO:4 is a p105 coding sequence codon-optimized for *E. coli*, SEQ ID NO:5 is a p105 coding sequence codon optimized for mammalian cell expression. Telomerase encoding nucleic acids may be part of human telomerase-expression vectors and may be incorporated into recombinant host cells, e.g. for expression and screening, transgenic animals, e.g. for functional studies such as the efficacy of candidate drugs for disease associated with human telomerase-mediated signal transduction, etc. Expression systems are selected and/or tailored to effect human telomerase protein structural and functional variants through alternative post-translational processing.

The invention also provides nucleic acid hybridization probes and replication/amplification primers having a human telomerase cDNA specific sequence contained in SEQ ID NO:3, bases 1-2345, and sufficient to effect specific hybridization thereto (i.e. specifically hybridize with SEQ ID NO:3, bases 1-2345 in the presence of natural ciliate telomerase cDNA, preferably in the presence of non-mammalian telomerase cDNA and more preferably, in the presence of murine telomerase cDNA). Demonstrating specific hybridization generally requires stringent conditions, for example, hybridizing in a buffer comprising 30% formamide in 5 x SSPE (0.18 M NaCl, 0.01 M NaPO₄, pH7.7,

0.001 M EDTA) buffer at a temperature of 42°C and remaining bound when subject to washing at 42°C with 0.2 x SSPE; preferably hybridizing in a buffer comprising 50% formamide in 5 x SSPE buffer at a temperature of 42°C and remaining bound when subject to washing at 42°C with 0.2 x SSPE buffer at 42°C. Human telomerase cDNA homologs can also be distinguished from other protein using alignment algorithms, such as BLASTX (Altschul *et al.* (1990) Basic Local Alignment Search Tool, J Mol Biol 215, 403-410).

The invention also provides non-natural sequence and isolated natural sequence human telomerase RNA. Natural human telomerase RNA sequences include the nucleic acid disclosed as SEQ ID NO:6, or a fragment thereof sufficient to specifically hybridize with a nucleic acid having the sequence defined by SEQ ID NO:6. Such fragments necessarily distinguish the previously described (Feng *et al.* 1995, Science 269, 1236-1241) human RNA species. Preferred such fragments comprise SEQ ID NO:6, bases 191-210, bases 245-259, bases 341-369 or bases 381-399. Non-natural sequences include derivatives and/or mutations of SEQ ID NO:6, where such derivatives/mutations provide alteration in template, protein binding, or other regions to effect altered telomerase substrate specificity or altered reaction product (e.g. any predetermined sequence), etc.; see, e.g. Autexier *et al.*, 1994, Genes & Develop 8, 563-575; Collins *et al.* (1995) EMBO J. 14, 5422-5432; Greider *et al.* (1995) Structure and Biochemistry of Ciliate and Mammalian Telomerases, in DNA Replication, DePamphilis, Ed., Cold Spring Harbor Laboratory Press. Additional derivatives function as dominant negative fragments which effectively compete for telomerase assembly. For examples, SEQ ID NO:7, 8 and 9 are derivatives which provide for modified substrate specificity and polymerase reaction product to interfere with cellular function (see, e.g. Hanish *et al.* (1994) Proc Natl Acad Sci 91, 8861-8865).

The subject nucleic acids are of synthetic/non-natural sequences and/or are isolated, i.e. unaccompanied by at least some of the material with which it is associated in its natural state, preferably constituting at least about 0.5%, preferably at least about 5% by weight of total nucleic acid present in a given fraction, and usually recombinant, meaning they comprise a non-natural sequence or a natural sequence joined to nucleotide(s) other than that which it is joined to on a natural chromosome. Nucleic acids comprising the nucleotide sequence of SEQ ID NO:3 or fragments thereof, contain

such sequence or fragment at a terminus, immediately flanked by a sequence other than that which it is joined to on a natural chromosome, or flanked by a native flanking region fewer than 10 kb, preferably fewer than 2 kb, which is immediately flanked by a sequence other than that which it is joined to on a natural chromosome. While the nucleic acids are usually RNA or DNA, it is often advantageous to use nucleic acids comprising other
5 bases or nucleotide analogs to provide modified stability, etc. The subject nucleic acids find a wide variety of applications including use as translatable transcripts, hybridization probes, PCR primers, diagnostic nucleic acids, etc.; use in detecting the presence of human telomerase genes and gene transcripts and in detecting or amplifying nucleic acids encoding additional human telomerase homologs and structural analogs.

10 In diagnosis, human telomerase hybridization probes find use in identifying wild-type and mutant human telomerase alleles in clinical and laboratory samples. Mutant alleles are used to generate allele-specific oligonucleotide (ASO) probes for high-throughput clinical diagnoses. In therapy, therapeutic human telomerase nucleic acids are used to modulate cellular expression or intracellular concentration or availability of active
15 telomerase. A wide variety of indications may be treated, either prophylactically or therapeutically with the subject compositions. For example, where limitation of cell growth is desired, e.g. neoproliferative disease, a reduction in telomerase expression is effected by introducing into the targeted cell type human telomerase nucleic acids which reduce the functional expression of human telomerase gene products (e.g. nucleic acids
20 capable of inhibiting translation of a functional telomerase transcript). Conditions for treatment include various cancers, where any of a wide variety of cell types may be involved, restenosis, where vascular smooth muscle cells are involved, inflammatory disease states, where endothelial cells, inflammatory cells and glomerular cells are involved, myocardial infarction, where heart muscle cells are involved, glomerular
25 nephritis, where kidney cells are involved, transplant rejection where endothelial cells are involved, infectious diseases such as HIV infection where certain immune cells and other infected cells are involved, or the like.

Telomerase inhibitory nucleic acids are typically antisense: single-stranded
sequences comprising complements of the disclosed natural telomerase coding sequences.
30 Antisense modulation of the expression of a given telomerase protein may employ telomerase antisense nucleic acids operably linked to gene regulatory sequences. Cell are

transfected with a vector comprising a human telomerase sequence with a promoter
sequence oriented such that transcription of the gene yields an antisense transcript capable
of binding to endogenous human telomerase protein encoding mRNA. Transcription of
the antisense nucleic acid may be constitutive or inducible and the vector may provide for
stable extrachromosomal maintenance or integration. Alternatively, single-stranded
5 antisense nucleic acids that bind to genomic DNA or mRNA encoding a given human
telomerase protein may be administered to the target cell, in or temporarily isolated from
a host, at a concentration that results in a substantial reduction in expression of the
targeted protein.

In other indications, e.g. certain hypersensitivities, atrophic diseases, etc., an
10 increase in cell growth or proliferation is desired. In these applications, an enhancement
in human telomerase expression is effected by introducing into the targeted cell type
human telomerase nucleic acids which increase the functional expression of human
telomerase gene products. Conditions for treatment include multiple sclerosis, where
certain neuronal cells are involved, inflammatory disease states such as rheumatoid
15 arthritis, where bystander cells are involved, transplant rejection where graft cells are
involved, infectious diseases such as HIV infection where certain uninfected host cells are
involved, or the like. Such nucleic acids may be human telomerase expression vectors,
vectors which upregulate the functional expression of an endogenous human telomerase
allele, or replacement vectors for targeted correction of human telomerase mutant alleles.

20 Various techniques may be employed for introducing of the nucleic acids into
viable cells, e.g. transfection with a retrovirus, viral coat protein-liposome mediated
transfection. The techniques vary depending upon whether one is using the subject
compositions in culture or *in vivo* in a host. In some situations it is desirable to provide
the nucleic acid source with an agent which targets the target cells, such as an antibody
25 specific for a surface membrane protein on the target cell, a ligand for a receptor on the
target cell, etc. Where liposomes are employed, proteins which bind to a surface
membrane protein associated with endocytosis may be used for targeting and/or to
facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type,
antibodies for proteins which undergo internalization in cycling, proteins that target
30 intracellular localization and enhance intracellular half-life.

The invention provides methods and compositions for enhancing the yield of

many recombinantly produced proteins by increasing maximum cell densities and survival time of host production cells in culture. Specifically, cultured cells are transfected with nucleic acids which effect the up-regulation of endogenous telomerase or the expression of an exogenous telomerase. For example, nucleic acids encoding functional human telomerase operably linked to a transcriptional promoter are used to over-express the exogenous telomerase in the host cell. Telomerase-expressing cells demonstrate enhanced survival ability at elevated cell densities and over extended culture periods.

The invention provides efficient methods of identifying agents, compounds or lead compounds for agents active at the level of a human telomerase modulatable cellular function. Generally, these screening methods involve assaying for compounds which modulate human telomerase interaction with a natural human telomerase binding target. A wide variety of assays for binding agents are provided including labeled in vitro telomere polymerase assays, protein-protein binding assays, immunoassays, cell based assays, etc. The methods are amenable to automated, cost-effective high throughput screening of chemical libraries for lead compounds. Identified reagents find use in the pharmaceutical industries for animal and human trials; for example, the reagents may be derivatized and rescreened in *in vitro* and *in vivo* assays to optimize activity and minimize toxicity for pharmaceutical development. Target indications may include infection, genetic disease, cell growth and regulatory disfunction, such as neoplasia, inflammation, hypersensitivity, etc. Target cells also include progenitor cells for repopulating blood or bone marrow, tissue grafts, and tissue subject to degradation/high turnover such as digestive and vascular endothelia and pulmonary and dermal epithelia.

In vitro binding assays employ a mixture of components including a human telomerase protein, which may be part of multi-subunit telomerase, a fusion product with another peptide or polypeptide, e.g. a tag for detection or anchoring, etc. The assay mixtures comprise a natural intracellular human telomerase binding target, e.g. a substrate. While native binding targets may be used, it is frequently preferred to use portions (e.g. peptides, nucleic acid fragments) thereof so long as the portion provides binding affinity and avidity to the subject human telomerase conveniently measurable in the assay. The assay mixture also comprises a candidate pharmacological agent. Candidate agents encompass numerous chemical classes, though typically they are organic compounds; preferably small organic compounds and are obtained from a wide

variety of sources including libraries of synthetic or natural compounds. A variety of other reagents may also be included in the mixture. These include reagents like salts, buffers, neutral proteins, e.g. albumin, detergents, protease inhibitors, nuclease inhibitors, antimicrobial agents, etc. may be used.

5 The resultant mixture is incubated under conditions whereby, but for the presence of the candidate pharmacological agent, the human telomerase specifically binds the cellular binding target, portion or analog with a reference binding affinity. The mixture components can be added in any order that provides for the requisite bindings and incubations may be performed at any temperature which facilitates optimal binding. Incubation periods are likewise selected for optimal binding but also minimized to
10 facilitate rapid, high-throughput screening.

After incubation, the agent-biased binding between the human telomerase and one or more binding targets is detected by any convenient way. For cell-free binding type assays, a separation step is often used to separate bound from unbound components. Separation may be effected by precipitation (e.g. TCA precipitation, immunoprecipitation,
15 etc.), immobilization (e.g. on a solid substrate), etc., followed by washing by, for examples, membrane filtration (e.g. Whatman's P-81 ion exchange paper, Polyfiltronic's hydrophobic GFC membrane, etc.), gel chromatography (e.g. gel filtration, affinity, etc.). For telomere polymerase assays, binding is detected by a change in the polymerization by the telomerase of a nucleic acid or nucleic acid analog on the substrate.

20 Detection may be effected in any convenient way. For cell-free binding assays, one of the components usually comprises or is coupled to a label. The label may provide for direct detection as radioactivity, luminescence, optical or electron density, etc. or indirect detection such as an epitope tag, an enzyme, etc. A variety of methods may be used to detect the label depending on the nature of the label and other assay components,
25 e.g. through optical or electron density, radiative emissions, nonradiative energy transfers, etc. or indirectly detected with antibody conjugates, etc.

A difference in the binding affinity of the human telomerase protein to the target in the absence of the agent as compared with the binding affinity in the presence of the agent indicates that the agent modulates the binding of the human telomerase protein to
30 the human telomerase binding target. Analogously, in the cell-based transcription assay also described below, a difference in the human telomerase transcriptional induction in the

presence and absence of an agent indicates the agent modulates human telomerase-induced transcription. A difference, as used herein, is statistically significant and preferably represents at least a 50%, more preferably at least a 90% difference.

The following examples are offered by way of illustration and not by way of limitation.

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EXAMPLES

1. Protocol for high-throughput human telomere polymerization assay.

A. Reagents:

- Neutralite Avidin: 20 µg/ml in PBS.
- human telomerase: 10^{-8} - 10^{-5} M human telomerase in PBS.
- Blocking buffer: 5% BSA, 0.5% Tween 20 in PBS; 1 hour at room temperature.
- Assay Buffer: 100 mM KCl, 20 mM HEPES pH 7.6, 1 mM MgCl₂, 1 mM dATP, 1 mM dTTP, 1% glycerol, 0.5% NP-40, 50 mM BME, 1 mg/ml BSA, cocktail of protease inhibitors.

15

- [³²P]α-dGTP 10x stock: 2×10^{-4} M "cold" dGTP with 100 µCi [³²P]α-dGTP.

Place in the 4°C microfridge during screening.

- telomerase substrate: 10^{-7} - 10^{-4} M biotinylated telomerase substrate (5'-biotin-d(TTAGGG)₃-3') in PBS.

20

- Protease inhibitor cocktail (1000X): 10 mg Trypsin Inhibitor (BMB # 109894), 10 mg Aprotinin (BMB # 236624), 25 mg Benzamidine (Sigma # B-6506), 25 mg Leupeptin (BMB # 1017128), 10 mg APMSF (BMB # 917575), and 2mM NaVO₃ (Sigma # S-6508) in 10 ml of PBS.

B. Preparation of assay plates:

25

- Coat with 120 µl of stock N Avidin per well overnight at 4°C.
- Wash 2 times with 200 µl PBS.
- Block with 150 µl of blocking buffer.
- Wash 2 times with 200 µl PBS.

C. Assay:

30

- Add 40 µl assay buffer/well.
- Add 40 µl human telomerase (1-1000 fmoles/40 ul in assay buffer)
- Add 10 µl compound or extract.

- Add 10 μ l [32 P] α -dGTP 10x stock.
- Add 40 μ l biotinylated telomerase substrate (0.1-10 pmoles/40 μ l in assay buffer)
- Shake at 25°C for 15 minutes.
- Incubate additional 45 minutes at 25°C.
- Stop the reaction by washing 4 times with 200 μ l PBS.
- Add 150 μ l scintillation cocktail.
- Count in Topcount.

D. Controls for all assays (located on each plate):

- a. Non-specific binding
- b. cold dGTP at 80% inhibition.

2. Protocol for high throughput human telomerase subunit- RNA complex formation assay.

A. Reagents:

- Neutralite Avidin: 20 μ g/ml in PBS.
- Blocking buffer: 5% BSA, 0.5% Tween 20 in PBS; 1 hour at room temperature.
- Assay Buffer: 100 mM KCl, 20 mM HEPES pH 7.6, 1 mM MgCl₂, 1% glycerol, 0.5% NP-40, 50 mM β -mercaptoethanol, 1 mg/ml BSA, cocktail of protease inhibitors.
- 32 P human telomerase protein 10x stock: 10^{-8} - 10^{-6} M "cold" human telomerase subunit (p105) supplemented with 200,000-250,000 cpm of labeled human telomerase (Beckman counter). Place in the 4°C microfridge during screening.
- Protease inhibitor cocktail (1000X): 10 mg Trypsin Inhibitor (BMB # 109894), 10 mg Aprotinin (BMB # 236624), 25 mg Benzamidine (Sigma # B-6506), 25 mg Leupeptin (BMB # 1017128), 10 mg APMSF (BMB # 917575), and 2mM NaVO₃ (Sigma # S-6508) in 10 ml of PBS.
- telomerase RNA: 10^{-7} - 10^{-4} M biotinylated RNA (SEQ ID NO:6) in PBS.

B. Preparation of assay plates:

- Coat with 120 μ l of stock N-Avidin per well overnight at 4°C.
- Wash 2 times with 200 μ l PBS.
- Block with 150 μ l of blocking buffer.
- Wash 2 times with 200 μ l PBS.

C. Assay:

- Add 40 μ l assay buffer/well.
- Add 10 μ l compound or extract.
- Add 10 μ l 32 P-human telomerase protein (20,000-25,000 cpm/0.1-10 pmoles/well
= 10^{-9} - 10^{-7} M final concentration).
- Shake at 25°C for 15 minutes.
- Incubate additional 45 minutes at 25°C.
- Add 40 μ l biotinylated RNA (0.1-10 pmoles/40 μ l in assay buffer)
- Incubate 1 hour at room temperature.
- Stop the reaction by washing 4 times with 200 μ l PBS.
- Add 150 μ l scintillation cocktail.
- Count in Topcount.

- D. Controls for all assays (located on each plate):
- a. Non-specific binding
 - b. Soluble (non-biotinylated telomerase) at 80% inhibition.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(I) APPLICANT: CAO, Zhaodan

5

(ii) TITLE OF INVENTION: Human Telomerase

(iii) NUMBER OF SEQUENCES: 10

10

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Science & Technology Law Group

(B) STREET: 268 Bush Street, Suite 3200

(C) CITY: San Francisco

(D) STATE: CA

15

(E) COUNTRY: USA

(F) ZIP: 94104

(v) COMPUTER READABLE FORM:

20

(A) MEDIUM TYPE: Floppy disk

(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:

25

(A) APPLICATION NUMBER:

(B) FILING DATE:

(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

30

(A) NAME: Osman Ph.D., Richard A

(B) REGISTRATION NUMBER: 36,627

(C) REFERENCE/DOCKET NUMBER: T96-005

(ix) TELECOMMUNICATION INFORMATION:

35

(A) TELEPHONE: (415) 343-4341

(B) TELEFAX: (415) 343-4342

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 759 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Met Ala Gly Leu Thr Leu Phe Val Gly Arg Leu Pro Pro Ser Ala Arg
 1 5 10 15
 Ser Glu Gln Leu Glu Glu Leu Phe Ser Gln Val Gly Pro Val Lys Gln
 20 25 30
 Cys Phe Val Val Thr Glu Lys Gly Ser Lys Ala Cys Arg Gly Phe Gly
 35 40 45
 Tyr Val Thr Phe Ser Met Leu Glu Asp Val Gln Arg Ala Leu Lys Glu
 50 55 60
 Ile Thr Thr Phe Glu Gly Cys Lys Ile Asn Val Thr Val Ala Lys Lys
 65 70 75 80
 Lys Leu Arg Asn Lys Thr Lys Glu Lys Gly Lys Asn Glu Asn Ser Glu
 85 90 95
 Cys Pro Lys Lys Glu Pro Lys Ala Lys Lys Ala Lys Val Ala Asp Lys
 100 105 110
 Lys Ala Arg Leu Ile Ile Arg Asn Leu Ser Phe Lys Cys Ser Glu Asp
 115 120 125
 Asp Leu Lys Thr Val Phe Ala Gln Phe Gly Ala Val Leu Glu Val Asn
 130 135 140
 Ile Pro Arg Lys Pro Asp Gly Lys Met Arg Gly Phe Gly Phe Val Gln
 145 150 155 160
 Phe Lys Asn Leu Leu Glu Ala Gly Lys Ala Leu Lys Gly Met Asn Met
 165 170 175
 Lys Glu Ile Lys Gly Arg Thr Val Ala Val Asp Trp Ala Val Ala Lys
 180 185 190
 Asp Lys Tyr Lys Asp Thr Gln Ser Val Ser Ala Ile Gly Glu Glu Lys
 195 200 205
 Ser His Glu Ser Lys His Gln Glu Ser Val Lys Lys Lys Gly Arg Glu

210 215 220
 Glu Glu Asp Met Glu Glu Glu Glu Asn Asp Asp Asp Asp Asp Asp
 225 230 235 240
 Asp Glu Glu Asp Gly Val Phe Asp Asp Glu Asp Glu Glu Glu Asn
 245 250 255
 5 Ile Glu Ser Lys Val Thr Lys Pro Val Gln Ile Gln Lys Arg Ala Val
 260 265 270
 Lys Arg Pro Ala Pro Ala Lys Ser Ser Asp His Ser Glu Glu Asp Ser
 275 280 285
 Asp Leu Glu Glu Ser Asp Ser Ile Asp Asp Gly Glu Glu Leu Ala Gln
 10 290 295 300
 Ser Asp Thr Ser Thr Glu Glu Gln Glu Asp Lys Ala Val Gln Val Ser
 305 310 315 320
 Asn Lys Lys Lys Arg Lys Leu Pro Ser Asp Val Asn Glu Gly Lys Thr
 325 330 335
 15 Val Phe Ile Arg Asn Leu Ser Phe Asp Ser Glu Glu Glu Glu Leu Gly
 340 345 350
 Glu Leu Leu Gln Gln Phe Gly Glu Leu Lys Tyr Val Arg Ile Val Leu
 355 360 365
 His Pro Asp Thr Glu His Ser Lys Gly Cys Ala Phe Ala Gln Phe Met
 20 370 375 380
 Thr Gln Glu Ala Ala Gln Lys Cys Leu Leu Ala Ala Ser Pro Glu Asn
 385 390 395 400
 Glu Ala Gly Gly Leu Lys Leu Asp Gly Arg Gln Leu Lys Val Asp Leu
 405 410 415
 25 Ala Val Thr Arg Asp Glu Ala Ala Lys Leu Gln Thr Thr Lys Val Lys
 420 425 430
 Lys Pro Thr Gly Thr Arg Asn Leu Tyr Leu Ala Arg Glu Gly Leu Ile
 435 440 445
 Arg Ala Gly Thr Lys Ala Ala Glu Gly Val Ser Ala Ala Asp Met Ala
 30 450 455 460
 Lys Arg Glu Arg Phe Glu Leu Leu Lys His Gln Lys Leu Lys Asp Gln
 465 470 475 480
 Asn Ile Phe Val Ser Arg Thr Arg Leu Cys Leu His Asn Leu Pro Lys
 485 490 495
 35 Ala Val Asp Asp Lys Gln Leu Arg Lys Leu Leu Leu Ser Ala Thr Ser
 500 505 510
 Gly Glu Lys Gly Val Arg Ile Lys Glu Cys Arg Val Met Arg Asp Leu

(2) INFORMATION FOR SEQ ID NO:2:

35

- (A) LENGTH: 2277 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

5	ATGGCNGGNY TNACNYTNTT YGTNGGNGMN YTNCCNCCNW SNGCNMGNWS NGARCARYTN	60
	GARGARYTNT TYWSNCARGT NGGNCCNGTN AARCARTGYT TYGTNGTNAC NGARAARGGN	120
	WSNAARGCNT GYMNGGGNTT YGNTAYOTN ACNTTYWSNA TGYTNGARGA YGTNCARMGN	180
	GCNYTNAARG ARATHACNAC NTTYGARGGN TGYAARATHA AYGTNACNGT NGCNAARAAR	240
	AARYTMGNA AYAARACNAA RGARAARGGN AARAAYGARA AYWSNGARTG YCCNAARAAR	300
10	GARCCNAARG CNAARAARGC NAARGTNGCN GAYAARAARG CNMGNYTNAT HATHMGNAAY	360
	YTNWSNTTYA ARTGYWSNGA RGAYGAYYTN AARACNGTNT TYGCNCARTT YGGNGCNGTN	420
	YTINGARGTNA AYATHCCNMG NAARCCNGAY GGNAAATGM GNGGNTTYGG NTTYGTNCAR	480
	TTYAARAAYY TNYTNGARGC NGGNAARGCN YTNAARGGNA TGAAYATGAA RGARATHAAR	540
	GGNMGNAACNG TNGCNGTNGA YTGCGCNGTN GCNAARGAYA ARTAYAARGA YACNCARWSN	600
15	GTNWSNGCNA THGGNGARGA RAARWSNCAY GARWSNAARC AYCARGARWS NGTNAARAAR	660
	AARGGNGMGNG ARGARGARGA YATGGARGAR GARGARAAYG AYGAYGAYGA YGAYGAYGAY	720
	GAYGARGARG AYGGNGTNTT YGAYGAYGAR GAYGARGARG ARGARAAYAT HGARWSNAAR	780
	GTNACNAARC CNGTNCARAT HCARAARMGN GCNGTNAARM GNCCNGCNCC NGCNAARWSN	840
	WSNGAYCAYW SNGARGARGA YWSNGAYYTN GARGARWSNG AYWSNATHGA YGAYGGNGAR	900
20	GARYTNGCNC ARWSNGAYAC NWSNACNGAR GARCARGARG AYAARGCNGT NCARGTNWSN	960
	AAYAARAARA ARMGNAARYT NCCNWSNGAY GTNAAYGARG GNAARACNGT NTTYATHMGN	1020
	AAYYTNSNT TYGAYWSNGA RGARGARGAR YTNGGNGARY TNYTNCARCA RTTYGGNGAR	1080
	YTNAARTAYG TNMGNATHGT NYTNCAYCCN GAYACNGARC AYWSNAARGG NTGYGCNTTY	1140
	GCNCARTTYA TGACNCARGA RGCGNCNCAR AARTGYTYNY TNGCNGCNWS NCCNGARAAY	1200
25	GARGCNGGNG GNYTNAARYT NGAYGGNGMN CARYTNAARG TNGAYYTNGC NGTNACNMGN	1260
	GAYGARGCNG CNAARYTNCA RACNACNAAR GTNAARAARC CNACNGGNAC NMGNAAYYTN	1320
	TAYYTNGCNM GNGARGGNYT NATHMGNGCN GGNACNAARG CNGCNGARGG NGTNWSNGCN	1380
	GCNGAYATGG CNAARMGNGA RMGNTTYGAR YTNYTNAARC AYCARAARYT NAARGAYCAR	1440
	AAYATHTTYG TNWSNMGNAC NMGNYTNTGY YTNCAYAAAY TNCCNAARGC NGTNGAYGAY	1500
30	AARCARYTNM GNAARYTYNT NYTNWSNGCN ACNWSNGGNG ARAARGGNGT NMGNATHAAR	1560
	GARTGYMGNG TNATGMGNGA YYTNAARGGN GTNCAYGGNA AYATGAARGG NCARWSNYTN	1620
	GGNTAYGCNT TYGCNGARTT YCARGARCAY GARCAYGCNY TNAARGCNYT NMGNYTNATH	1680
	AAYAAYAAYC CNGARATHTT YGGNCCNYTN AARMGNCCNA THGTNGARTT YWSNYTNGAR	1740
	GAYMGNMGNA ARYTNAARAT GAARGARYTN MGNATHCARM GNWSNYTNCA RAARATGMGN	1800
35	WSNAARCCNG CNACNGGNGA RCCNCARAAR GGNCARCCNG ARCCNGCNAA RGAYCARCAR	1860
	CARAARGCNG CNCARCAYCA YACNGARGAR CARWSNAARG TNCCNCCNGA RCARAARMGN	1920
	AARGCNGGNW SNACNWSNTG GACNGGNTTY CARACNAARG CNGARGTNGA RCARGTNGAR	1980

YTNCNGAYG GNAARAARMG NMGNAARGTN YTNGCNYTNC CNWSNCAYMG NGGNCCNAAR 2040
 ATHMGNYTNM GNGAYAARGG NAARGTNAAR CCNGTNCAYC CNAARAARCC NAARCCNCAR 2100
 ATHAAYCART GGAARCARGA RAARCRCAR YTNWSNWSNG ARCARGTNWS NMGNAARAAR 2160
 GCNAARGGNA AYAARACNGA RACNMGNWTTT AAYCARYTNG TNGARCARTA YAARCARAAR 2220
 YTNYTNGGNC CNWSNAARGG NGCNCNNTYTN GCNAARMGNW SNAARTGGTT YGAYWSN 2277

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(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2733 base pairs

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(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

TGAGCTTGGT TGTCCTACCA AAGCCAGCGT TTCGGCTCGC GTGCGCCGGC CTAGTTTGCT 60
 CGCGTCTCTCA CGCGCTTTGG GTTTCCTCGT CTCATGGCCG GCCTGACCTT ATTTGTGGGC 120
 CGCCTCCCGC CCTCGGCCCG CAGTGAGCAG CTGGAGGAAC TGTTCAGTCA GGTGGGGCCG 180
 20 GTGAAGCAGT GCTTCGTGGT GACTGAAAAA GGGAGTAAGG CATGTCGAGG CTTTGGCTAT 240
 GTCACTTTTT CAATGCTGGA AGATGTTTCA AGGGCCCTCA AGGAGATTAC CACCTTTGAA 300
 GGTTGCAAGA TCAACGTGAC TGTTGCCAAG AAAAACTGA GGAACAAGAC AAAGGAAAAG 360
 GGGAAAAATG AAAACTCAGA GTGCCCAAAG AAGGAGCCGA AGGCTAAAAA AGCCAAAGTG 420
 GCAGATAAGA AAGCCAGATT AATTATTCCG AACCTGAGCT TTAAGTGTTT AGAAGATGAC 480
 25 TTGAAGACAG TATTTGCTCA ATTTGGAGCT GTCCTGGAAG TAAATATCCC TAGGAAACCA 540
 GATGGGAAGA TGCGCGGTTT TGGTTTTGTT CAGTTCAAAA ACCTCCTAGA AGCAGGTAAA 600
 GCTCTCAAAG GCATGAACAT GAAAGAGATA AAAGGCCGGA CAGTGGCTGT GGATTGGGCC 660
 GTGGCAAAGG ATAAATATAA AGATACACAG TCTGTTTCTG CTATAGGTGA GGAAAAGAGC 720
 CATGAATCTA AACATCAGGA ATCAGTTAAA AAGAAGGGCA GAGAGGAAGA GGATATGGAA 780
 30 GAGGAAGAAA ACGATGATGA TGACGATGAT GATGATGAAG AAGATGGGGT TTTTGATGAT 840
 GAAGATGAAG AGGAAGAGAA TATAGAATCA AAGGTGACCA AGCCTGTGCA AATTCAGAAG 900
 AGAGCAGTCA AGAGACCAGC CCCTGCAAAA AGCAGTGATC ATTCTGAGGA GGACAGTGAC 960
 CTAGAGGAAA GCGATAGTAT TGATGATGGA GAGGAACTGG CTCAGAGTGA TACCAGCACT 1020
 GAGGAGCAAG AGGATAAAGC TGTGCAAGTC TCAAACAAA AGAAGAGGAA ATTACCTCT 1080
 35 GATGTGAATG AAGGGAAAAC TGTTTTATC AGAAATCTGT CCTTTGACTC AGAAGAAGAA 1140
 GAACTTGGGG AGCTTCTCCA ACAGTTTGA GAACTCAAAT ATGTCCGCAT TGTCTTGCAT 1200
 CCAGACACAG AGCATTCTAA AGGTTGTGCA TTTGCCAGT TCATGACTCA AGAAGCAGCT 1260

CAGAAATGCC TTCTAGCTGC TTCTCCAGAG AATGAGGCTG GTGGGCTTAA ACTGGATGGC 1320
 CGGCAGCTCA AGGTTGACTT GCGCGTGACC CGTGATGAGG CTGCAAAGCT TCAGACGACG 1380
 AAGGTGAAGA AGCCGACTGG CACCCGGAAT CTCTATCTGG CCCGAGAAGG CTTGATTCTG 1440
 GCTGGGACGA AGGCTGCAGA GGGTGTGAGT GCTGCTGATA TGGCCAAAAG AGAACGGTTT 1500
 GAGCTGCTGA AGCATCAGAA ACTCAAGGAC CAGAATATCT TTGTCTCCCG AACCAGGCTC 1560
 5 TGCCTGCACA ATCTCCCAA GGCTGTAGAT GACAAACAGC TCAGAAAGCT GCTGCTGAGT 1620
 GCTACTAGTG GAGAGAAAGG GGTGCCATC AAGGAGTGTA GAGTGATGCC AGACCTCAA 1680
 GGAGTTCATG GGAACATGAA GGGTCAGTCC CTGGGCTACG CTTTGC GGA GTTCCAAGAG 1740
 CACGAGCATG CCCTGAAAGC CCTCCGCTC ATCAACAACA ATCCAGAAAT CTTTGGGCCT 1800
 CTGAAGAGAC CAATAGTGA GTTCTCTTA GAAGATCGAA GAAACTTAA AATGAAGGAA 1860
 10 TTAAGGATCC AGCGCAGCTT GCAAAAAATG AGATCCAAGC CTGCAACTGG TGAGCCTCAG 1920
 AAGGGGCAAC CAGAGCCTGC AAAAGACCAG CAACAGAAGG CAGCTCAACA CCACACAGAG 1980
 GAACAAAGCA AGGTGCCCCC AGAGCAGAAG AGAAAGGCGG GCTCTACCTC ATGGACCGGG 2040
 TTCCAGACCA AGGCTGAAGT GGAGCAGGTG GAGCTGCCTG ATGGAAAGAA GAGAAGAAAG 2100
 GTCTGGCGC TCCCCTCACA CCGAGGCCCC AAAATCAGGT TCGGGACAA AGGCAAAGTG 2160
 15 AAGCCCGTCC ATCCCAAAA GCCAAAGCCA CAGATAAACC AGTGGAGCA GGAGAAGCAG 2220
 CAATTATCGT CCGAGCAGGT ATCTAGGAAA AAAGCTAAGG GAAATAGAC GGAAACCCGC 2280
 TTCAACCAGC TGGTCGAACA ATATAAGCAG AAATTATTGG GACCTTCTAA AGGAGCACCT 2340
 CTTGCAAAGA GGAGCAAATG GTTTGATAGT TGATGATGGC AGCAGGCTGG GTAAGAAGCT 2400
 GGGTTGTATA CTTTCTGGTG ACACTCCTGG GCTCCTCCCC ATCCCCCGTG TCTCTCACTG 2460
 20 AGGGAAAGAA AATCCCCAAG GGCAGTCCA CTGTGCTCGG AGGTGCCCTG GACTGTGTAC 2520
 ATCTGAACTT TGGTCCATCC TTTGATGTGT GGTTCGTTAG CCACAAAGAG AAATATCTGA 2580
 AAGTCAACAT GATGCTTCTT GCATATTATC CAGATTATTG TATGAAGTTG TGTCTATAAT 2640
 TATTACCAAT TTTTATTCTT TATTCTCAA ATGGAAACAC CTGAAAAGC AAAAAAAAAA 2700
 AAAAAAAAAA CTCGAGGGGG GCCCGTACCC AAT 2733

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(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 2277 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

AUGGCUGGUC UGACCCUGUU CGUUGGUCGU CUGCCGCCGU CCGCUCGUUC CGAACAGCUG

60

	GAAGAACUGU UCUCCCAGGU UGGUCCGGUU AAACAGUGCU UCGUUGUAC CGAAAAAGGU	120
	UCCAAAGCUU GCCGUGGUUU CGGUUACGUU ACCUUCUCCA UGCUGGAAGA CGUUCAGCGU	180
	GCUCUGAAAG AAAUCACCAC CUUCGAAGGU UGCAAAAUCA ACGUUAACCGU UGCUAAAAAA	240
	AAACUGCGUA ACAAACCAA AGAAAAAGGU AAAACGAAA ACUCCGAAUG CCCGAAAAAA	300
	GAACCGAAAG CUAAAAAGC UAAAGUUGCU GACAAAAAG CUCGUCUGAU CAUCCGUAAAC	360
5	CUGUCCUUA AAUGCUCGA AGACGACCUG AAAACCGUUU UCGCUCAGUU CGGUGCUGUU	420
	CUGGAAGUUA ACAUCCCGCG UAAACCGGAC GGUAAAAUGC GUGGUUUCGG UUUCGUUCAG	480
	UUCAAAAACC UGCUGGAAGC UGGUAAAGCU CUGAAAGGUA UGAACAUGAA AGAAAUCAA	540
	GGUCGUACCG UUGCUGUGA CUGGGCUGUU GCUAAAGACA AAUACAAAGA CACCCAGUCC	600
	GUUCCGCUA UCGUGAAGA AAAUCCAC GAUCCAAAC ACCAGGAAUC CGUAAAAAA	660
10	AAAGGUCGUG AAGAAGAAGA CAUGGAAGAA GAAGAAACG ACGACGACGA CGACGACGAC	720
	GACGAAGAAG ACGGUGUUU CGACGACGAA GACGAAGAAG AAGAAAACAU CGAAUCCAAA	780
	GUUACCAAAC CGGUUCAGAU CCAGAAACGU GCUGUUAAC GUCCGGCUCG GGUUAAUCC	840
	UCCGACCACU CCGAAGAAGA CUCCGACCUG GAAGAAUCCG ACUCCAUCGA CGACGGUGAA	900
	GAACUGGCUC AGUCCGACAC CUCCACCGAA GAACAGGAAG ACAAGCUGU UCAGGUUUC	960
15	AACAAAAAA AACGUAAACU GCCGUCGAC GUUAACGAAG GUAAAACCGU UUUCAUCCGU	1020
	AACUGUCCU UCGACUCCGA AGAAGAAGAA CUGGGUGAAC UGCUGCAGCA GUUCGGUGAA	1080
	CUGAAUACG UUCGUADCGU UCUGCACCCG GACACCGAAC ACUCCAAAGG UUGCGCUUUC	1140
	GCUCAGUUA UGACCCAGGA AGCUGCUCAG AAUUGCCUGC UGGCUGCUUC CCCGAAAAAC	1200
	GAAGCUGGUG GUCUGAAACU GGACGGUCGU CAGCUGAAAG UUGACCUGGC UGUUACCCGU	1260
20	GACGAAGCUG CUAAACUGCA GACCACCAA GUUAAAAAC CGACCGUAC CCGUAACTUG	1320
	UACCUGGCUC GUGAAGGUCU GAUCCGUGCU GGUACCAAAG CUGCUGAAGG UGUUCCGCU	1380
	GCUGACAUGG CUAAACGUGA ACGUUUCGAA CUGCUGAAAC ACCAGAAACU GAAAGACCAG	1440
	AACAUUCUG UUUCCCGUAC CCGUCUGUGC CUGCACAACC UGCCGAAAGC UGUUGACGAC	1500
	AAACAGCUGC GUAAACUGCU GCUGUCCGU ACCUCCGGUG AAAAAGGUGU UCGUAUCAA	1560
25	GAAUGCCGUG UUAUGCGUGA CCUGAAAGGU GUUCACGGUA ACAUGAAAGG UCAGUCCUG	1620
	GGUACGCUU UCGCUGAAU CCAGGAACAC GAACACGCUC UGAAAGCUCU GCGUCUGAUC	1680
	AACAACAACC CGGAAUUCU CGGUCCGUG AAACGUCCGA UCGUUGAAU CUCCUGGAA	1740
	GACCGUCGUA AACUGAAAAU GAAAGAACUG CGUAUCCAGC GUUCCUGCA GAAAUGCGU	1800
	UCCAAACCGG CUACCGGUGA ACCGAGAAA GGUACGCCG AACCGGCUAA AGACCAGCAG	1860
30	CAGAAAGCUG CUCAGCACCA CACCGAAGAA CAGUCCAAAG UUCGCGCGGA ACAGAAACGU	1920
	AAAGCUGGU CCACUCCUG GACCGGUUUC CAGACCAAAG CUGAAGUGA ACAGGUUGAA	1980
	CUGCCGGACG GUAAAAACG UCGUAAAGU CUGGCUCUGC CGUCCACCG UGGUCCGAAA	2040
	AUCCGUCUGC GUGACAAAGG UAAAGUAAA CCGGUUCACC CGAAAAACC GAAACCGCAG	2100
	AUCAACCAGU GGAAACAGGA AAAACAGCAG CUGUCCUCG AACAGGUUUC CCGUAAAAAA	2160
35	GCUAAAGGUA ACAAACCGA AACCUGUUC AACCAGCUGG UUGAACAGUA CAAACAGAAA	2220
	CUGCUGGGUC CGUCCAAAGG UGCUCGCGU GCUAAACGU CCAAUGGUU CGACUCC	2277

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2277 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

10	ATGGCCGGCC TGACCCTGTT CGTGGGCCGC CTGCCCCCA GCGCCCGCAG CGAGCAGCTG	60
	GAGGAGCTGT TCAGCCAGGT GGGCCCCGTG AAGCAGTGCT TCGTGGTGAC CGAGAAGGGC	120
	AGCAAGGCCT GCCGCGGCTT CGGTACGTG ACCTTCAGCA TGCTGGAGGA CGTGCAGCGC	180
	GCCCTGAAGG AGATCACCAC CTTGAGGGC TGCAAGATCA ACGTGACCGT GGCCAAGAAG	240
15	AAGCTGCGCA ACAAGACCAA GGAGAAGGGC AAGAACGAGA ACAGCGAGTG CCCCAGAAG	300
	GAGCCCAAGG CCAAGAAGGC CAAGGTGGCC GACAAGAAGG CCCGCTGAT CATCCGCAAC	360
	CTGAGCTTCA AGTGCAGCGA GGACGACCTG AAGACCGTGT TCGCCAGTT CGGCGCCGTG	420
	CTGGAGGTGA ACATCCCCCG CAAGCCCGAC GGCAAGATGC GCGGCTTCGG CTTCGTGCAG	480
	TTCAAGAACC TGCTGGAGGC CGGCAAGGCC CTGAAGGGCA TGAACATGAA GGAGATCAAG	540
20	GGCCGCACCG TGCCGTGGA CTGGGCCGTG GCCAAGGACA AGTACAAGGA CACCAGAGC	600
	GTGAGCGCCA TCGGCGAGGA GAAGAGCCAC GAGAGCAAGC ACCAGGAGAG CGTGAAGAAG	660
	AAGGGCCGCG AGGAGGAGGA CATGGAGGAG GAGGAGAAGC ACGACGACGA CGACGACGAC	720
	GACGAGGAGG ACGGCGTGTT CGACGACGAG GACGAGGAGG AGGAGAACAT CGAGAGCAAG	780
	GTGACCAAGC CCGTGCAGAT CCAGAAGCGC GCCGTGAAGC GCCCCGCCCC CGCCAAGAGC	840
25	AGCGACCACA GCGAGGAGGA CAGCGACCTG GAGGAGAGCG ACAGCATCGA CGACGGCGAG	900
	GAGCTGGCCC AGAGCGACAC CAGCACCGAG GAGCAGGAGG ACAAGGCCGT GCAGGTGAGC	960
	AACAAGAAGA AGCGCAAGCT GCCCAGCGAC GTGAACGAGG GCAAGACCGT GTTCATCCGC	1020
	AACCTGAGCT TCGACAGCGA GGAGGAGGAG CTGGGCGAGC TGCTGCAGCA GTTCGGCGAG	1080
	CTGAAGTACG TGCGCATCGT GCTGCACCCC GACACCGAGC ACAGCAAGGG CTGCGCCTTC	1140
30	GCCCAGTTCA TGACCCAGGA GGCCGCCAG AAGTGCCTGC TGGCCGCCAG CCCCAGAAAC	1200
	GAGGCCGGCG GCCTGAAGCT GGACGGCCGC CAGCTGAAGG TGGACCTGGC CGTGACCCGC	1260
	GACGAGGCCG CCAAGCTGCA GACCACCAAG GTGAAGAAGC CCACCGGCAC CCGCAACCTG	1320
	TACCTGGCCC GCGAGGGCCT GATCCGCGCC GGCACCAAGG CCGCCGAGGG CGTGAGCGCC	1380
	GCCGACATGG CCAAGCGCGA GCGCTTCGAG CTGCTGAAGC ACCAGAAGCT GAAGGACCAG	1440
35	AACATCTTCG TGAGCCGCAC CCGCTGTGC CTGCACAACC TGCCCAAGGC CGTGGACGAC	1500
	AAGCAGCTGC GCAAGCTGCT GCTGAGCGCC ACCAGCGGCG AGAAGGGCGT GCGCATCAAG	1560
	GAGTGCCGCG TGATGCGCGA CCTGAAGGGC GTGCACGGCA ACATGAAGGG CCAGAGCCTG	1620

GGCTACGCCT TCGCCGAGTT CCAGGAGCAC GAGCACGCCC TGAAGGCCCT GCGCCTGATC 1680
 AACAAACAACC CCGAGATCTT CGGCCCCCTG AAGCGCCCCA TCGTGGAGTT CAGCCTGGAG 1740
 GACCGCCGCA AGCTGAAGAT GAAGGAGCTG CGCATCCAGC GCAGCCTGCA GAAGATGCGC 1800
 AGCAAGCCCCG CCACCGGCGA GCCCCAGAAG GGCCAGCCCCG AGCCCGCCAA GGACCAGCAG 1860
 CAGAAGGCCG CCCAGCACCA CACCGAGGAG CAGAGCAAGG TGCCCCCGA GCAGAAGCGC 1920
 5 AAGGCCGGCA GCACCAGCTG GACCGGCTTC CAGACCAAGG CCGAGGTGGA GCAGGTGGAG 1980
 CTGCCCGACG GCAAGAAGCG CCGCAAGGTG CTGGCCCTGC CCAGCCACCG CGCCCCAAG 2040
 ATCCGCCTGC GCGACAAGGG CAAGGTGAAG CCCGTGCRCC CCAAGAAGCC CAAGCCCCAG 2100
 ATCAACCAAGT GGAAGCAGGA GAAGCAGCAG CTGAGCAGCG AGCAGGTGAG CCGCAAGAAG 2160
 GCCAAGGGCA ACAAGACCGA GACCGGCTTC AACCAGCTGG TGGAGCAGTA CAAGCAGAAG 2220
 10 CTGCTGGGCC CCAGCAAGGG CGCCCCCTG GCCAAGCGCA GCAAGTGGTT CGACAGC 2277

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 540 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GGGTTGCGGA GGGTGGGCCT GGGAGGGGTG GTGGCCATTT TTTGTCTAAC CCTAACTGAG 60
 AAGGGCGTAG GCGCCGTGCT TTTGCTCCCC GCGCGCTGTT TTTCTCGCTG ACTTTCAGCG 120
 25 GCGGAAAAG CCTCGGCCTG CCGCCTTCCA CCGTTCATTC TAGAGCAAAC AAAAAATGTC 180
 AGCTGCTGGC CCGTTCGCCC CTCCCGGGGA CCTGCGGCGG GTCGCTGCC CAGCCCCCGA 240
 ACCCGGCCTG GAGGCCGCGG TCGGCCCGGG GCTTCTCCGG AGGCACCCAC TGCCACCGCG 300
 AAGAGTTGGG CTCTGTCAGC CGCGGCTCTC TCGGGGGCGA GGGCGAGGTT CAGGCCTTTC 360
 AGGCCGCGAGG AAGAGGAACG GAGCGAGTCC CCGCGCGCGG CGCGATTCCC TGAGCTGTGG 420
 30 GACGTGCACC CAGGACTCGG CTCACACATG CAGTTCGCTT TCCTGTTGGT GGGGGGAACG 480
 CCGATCGTGC GCATCCGTCA CCCCTCGCCG GCAGTGGGGG CTTGTGAACC CCCAAACCTG 540

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- 35 (A) LENGTH: 540 base pairs
 (B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

5 GGGTTGCGGA GGGTGGGCCT GGGAGGGGTG GTGGCCATT TTTGTCCAAC CCCAACTGAG 60
AAGGGCGTAG GCGCCGTGCT TTTGCTCCCC GCGCGCTGTT TTTCTCGCTG ACTTTCAGCG 120
GGCGGAAAAG CCTCGGCCTG CCGCCTTCCA CCGTTCATTC TAGAGCAAAC AAAAAATGTC 180
AGCTGCTGGC CCGTTCGCCC CTCCCGGGGA CTGCGGCGG GTCGCCTGCC CAGCCCCCGA 240
10 ACCCCGCCTG GAGGCCGCGG TCGGCCCGGG GCTTCTCCGG AGGCACCCAC TGCCACCGCG 300
AAGAGTTGGG CTCTGTCAGC CGCGGGTCTC TCGGGGCGA GGGCGAGGTT CAGGCCTTTC 360
AGGCCGAGG AAGAGGAACG GAGCGAGTCC CCGCGCGCGG CGCGATTCCC TGAGCTGTGG 420
GACGTGCACC CAGGACTCGG CTCACACATG CAGTTCGCTT TCCTGTTGGT GGGGGGAACG 480
CCGATCGTGC GCATCCGTCA CCCCTCGCCG GCAGTGGGGG CTTGTGAACC CCCAAACCTG 540

15

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 540 base pairs

20

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GGGTTGCGGA GGGTGGGCCT GGGAGGGGTG GTGGCCATT TTTGTCTAAG CCTAAGTGAG 60
AAGGGCGTAG GCGCCGTGCT TTTGCTCCCC GCGCGCTGTT TTTCTCGCTG ACTTTCAGCG 120
GGCGGAAAAG CCTCGGCCTG CCGCCTTCCA CCGTTCATTC TAGAGCAAAC AAAAAATGTC 180
30 AGCTGCTGGC CCGTTCGCCC CTCCCGGGGA CTGCGGCGG GTCGCCTGCC CAGCCCCCGA 240
ACCCGCCTG GAGGCCGCGG TCGGCCCGGG GCTTCTCCGG AGGCACCCAC TGCCACCGCG 300
AAGAGTTGGG CTCTGTCAGC CGCGGGTCTC TCGGGGCGA GGGCGAGGTT CAGGCCTTTC 360
AGGCCGAGG AAGAGGAACG GAGCGAGTCC CCGCGCGCGG CGCGATTCCC TGAGCTGTGG 420
GACGTGCACC CAGGACTCGG CTCACACATG CAGTTCGCTT TCCTGTTGGT GGGGGGAACG 480
35 CCGATCGTGC GCATCCGTCA CCCCTCGCCG GCAGTGGGGG CTTGTGAACC CCCAAACCTG 540

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 538 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGGTTGCGGA GGGTGGGCCT GGGAGGGGTG GTGGCCATT TTTGTCTACC CTACTGAGAA 60
 GGGCGTAGGC GCCGTGCTTT TGCTCCCGC GCGCTGTTTT TCTCGCTGAC TTTCAGCGGG 120
 CGGAAAAGCC TCGGCCTGCC GCCTTCCACC GTTCATTCTA GAGCAAACAA AAAATGTCTAG 180
 CTGCTGGCCC GTTCGCCCCCT CCCGGGGACC TCGCGCGGGT CGCCTGCCCA GCCCCCGAAC 240
 CCCGCCTGGA GGCCGCGGTC GGCCCGGGGC TTCTCCGGAG GCACCCACTG CCACCCGCGAA 300
 GAGTTGGGCT CTGTCTAGCCG CGGGTCTCTC GGGGGCGAGG GCGAGGTCA GGCCTTTCAG 360
 GCCGCAGGAA GAGGAACGGA GCGAGTCCCC GCGCGCGGCG CGATTCCCTG AGCTGTGGGA 420
 CGTGACACCA GGAATCGGCT CACACATGCA GTTCGCTTTC CTGTTGGTGG GGGGAACGCC 480
 GATCGTGCGC ATCCGTCACC CCTCGCCGGC AGTGGGGGCT TGTGAACCCC CAAACCTG 538

15

(2) INFORMATION FOR SEQ ID NO:10:

20

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: not relevant
 (D) TOPOLOGY: not relevant

25

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

- (A) NAME/KEY: Peptide
 (B) LOCATION: 5..13
 (D) OTHER INFORMATION: /note= "Xaa represents isoleucine
 or leucine"

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Glu Ala Ala Thr Xaa Asp Xaa Pro Gln Gln Gly Ala Asn Lys

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WHAT IS CLAIMED IS:

1. An isolated nucleic acid comprising SEQ ID NO:3, or a portion thereof encoding a telomerase protein p105 (SEQ ID NO:1) domain having human telomerase-specific activity.
2. An isolated nucleic acid according to claim 1, wherein said domain specifically binds at least one of the telomerase RNA of SEQ ID NO: 6, a telomerase subunit, substrate, agonist, antagonist, chaperone, regulatory protein or cytoskeletal protein.
3. An isolated nucleic acid comprising a portion of SEQ ID NO: 3, bases 1-2345, which specifically hybridizes with, or amplifies from a nucleic acid having the sequence defined by SEQ ID NO:3.
4. A method of modulating the expression of a telomerase transcript, said method comprising steps: contacting inside a cell an endogenous transcript encoding a telomerase protein with a nucleic acid according to claim 3 under conditions whereby said nucleic acid hybridizes with said transcript, whereby the expression of said transcript is modulated.
5. A recombinant nucleic acid consisting of an open reading frame comprising SEQ ID NO:3, or a portion thereof sufficient to encode a telomerase protein p105 (SEQ ID NO:1) domain having human telomerase-specific activity.
6. A recombinant nucleic acid according to claim 5, wherein said open reading frame comprises SEQ ID NO:3, bases 97-2370.
7. A cell comprising a nucleic acid according to claim 5.
8. A method of making an isolated telomerase protein, comprising steps: introducing a nucleic acid according to claim 5 into a host cell or cellular extract, incubating said host cell or extract under conditions whereby said nucleic acid is expressed as a transcript and said transcript is expressed as a translation product comprising said protein, and isolating said translation product.

9. An isolated human telomerase made by the method of claim 8.

10. A method of screening for an agent which modulates the binding of a human telomerase to a binding target, said method comprising the steps of:

5 translating the nucleotide sequence of SEQ ID NO:3 of a nucleic acid according to claim 5 to obtain a human telomerase protein domain;

incubating a mixture comprising:

a telomerase or telomerase protein comprising said domain,

a binding target of said telomerase protein, and

a candidate agent;

10 under conditions whereby, but for the presence of said agent, said telomerase or telomerase protein specifically binds said binding target at a reference affinity;

detecting the binding affinity of said telomerase or telomerase protein to said binding target to determine an agent-biased affinity,

15 wherein a difference between the agent-biased affinity and the reference affinity indicates that said agent modulates the binding of said telomerase or telomerase protein to said binding target.

11. A method according to claim 10, wherein said binding target is a substrate of said telomerase and said reference and agent-biased binding affinity are each detected as the
20 polymerization by said telomerase of a nucleic acid on said substrate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12297

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/194, 240.1, 252.3, 320.1, 69.1, 91.3, 172.3, 7.1; 530/350; 536/23.1, 23.2, 24.31, 24.33

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,583,016 A (VILLEPONTEAU et al.) 10 December 1996, entire patent, especially the abstract and column 20 lines 10-60.	1-11
Y	WO 96/19580 A2 (COLD SPRING HARBOR LABORATORY) 27 June 1996. See abstract and examples 7-10.	1-11
Y	COUNTER et al. Telomerase Activity in Human Ovarian Carcinoma. Proc. Natl. Acad. Sci. USA. April 1994. Vol 91, pages 2900-2904, see entire article.	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"A" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

05 SEPTEMBER 1997

Date of mailing of the international search report

31 OCT 1997

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12297

A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

C12N 9/12, 5/00, 1/20, 15/00; C12P 21/06, 19/34; C07K 1/00; C07H 21/02, 21/04

A. CLASSIFICATION OF SUBJECT MATTER: US CL :

435/194, 240.1, 252.3, 320.1, 69.1, 91.3, 172.3, 7.1; 530/350; 536/23.1, 23.2, 24.31, 24.33

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN Files : Medline, CaPlus, Biosis, Wpids, Biotechds & Seisearch. Search Terms: Telomerase and (DNA or RNA or Protein), and human, telomerase, etc. Protein and Nucleic acid data base search for amino acid and dna sequences.

Form PCT/ISA/210 (extra sheet)(July 1992)*